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What Comes First? Multitissue Involvement Leading to Radiographic Osteoarthritis

Magnetic Resonance Imaging–Based Trajectory Analysis Over Four Years in the Osteoarthritis Initiative

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Objective. **To assess whether the presence of structural osteoarthritis (OA) features over as many as 4 years prior to incident radiographic OA increases the risk of radiographic OA in a nested, case–control design.**

Methods. **We studied 355 knees from the Osteoarthritis Initiative cohort that developed radiographic OA before the 48-month visit. They were matched one-to-one by sex, age, and contralateral knee radiographic status with a control knee. Magnetic resonance images (MRIs) were read for bone marrow lesions (BMLs), cartilage damage, meniscal damage (including tears and extrusion), Hoffa synovitis, and effusion synovitis. Conditional logistic regression was applied to assess the risk of radiographic OA with regard to the presence of BMLs (score ≥2), cartilage lesions (score ≥1.1), meniscal damage (any) and extrusion of ≥3 mm ± (score ≥2), and Hoffa and effusion synovitis (any). Time points were defined as incident radiographic OA visit (P0), 1 year prior to the detection of radiographic OA (P −1), 2 years prior to the detection of radiographic OA (P −2), etc.**

Results. **The presence of Hoffa synovitis (hazard ratio [HR] 1.76 [95% confidence interval (95% CI) 1.18–2.64]), effusion synovitis (HR 1.81 [95% CI 1.18–2.78]), and medial meniscal damage (HR 1.83 [95% CI 1.17–2.89]) at P −2 predicted radiographic OA incidence. At P −1, all features but meniscal extrusion predicted radiographic OA, with highest odds for medial BMLs (HR 6.50 [95% CI 2.27–18.62]) and effusion synovitis (HR**

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2.50 [95% CI 1.76–3.54]). The findings at P −3 and P −4 did not reach statistical significance.

Conclusion. **Our findings indicate that the presence of specific structural features of MRI-detected joint damage 2 years prior to incident radiographic OA increases the risk of incident radiographic OA. However, 1 year prior to radiographic OA, the presence of almost any abnormal morphologic feature increases the risk of radiographic OA in the subsequent year.**

Osteoarthritis (OA) is a complex, heterogeneous condition that is the most common cause of disability in the aging population (1). The hallmarks of the pathophysiology of OA are the breakdown of cartilage and associated changes in adjacent soft tissue and subchondral bone that lead to debilitating joint symptoms such as pain and disability accompanied by structural deformity (1). As a consequence of OA, rates of knee replacement more than doubled in the US from 1999 to 2008 (2).

Imaging markers have been used as indirect surrogate measures of disease status and activity with variable plausibility and success (3,4). While radiography is only able to depict osseous tissue alterations and only in advanced stages of the disease, magnetic resonance imaging (MRI) provides insights concerning all involved joint tissues that are clinically relevant at a much earlier disease stage (5–7).

Knowledge about the early stages of knee OA is sparse. The accepted definition of OA is based on the presence of a definite osteophyte on the posteroanterior radiograph (defined as grade 2 on the Kellgren/Lawrence [K/L] scale) (3). However, large population-based studies applying MRI have suggested that structural joint pathology is widely present in persons without radiographic evidence of disease (5,6). The relevance of these morphologic abnormalities is not known, and some of them may be precursors of disease. A recent analysis based on a subset of the Osteoarthritis Initiative (OAI) cohort, a large ongoing observational study of knee OA, assessed subjects without radiographic OA at 2 defined time points, i.e., at 12 and 48 months, using cartilage loss and incident knee symptoms as the outcome parameters, and found that structural joint damage was associated with incident persistent symptoms and that more concomitant lesion types were associated with a greater risk of symptom outcomes and incident tibiofemoral cartilage damage (8). From this, the authors concluded that the observed findings are not incidental in persons at increased risk of OA and may represent early disease and illness. Studies examining multiple time points prior to disease onset are not available to date.

Given that MRI features often coexist in knees with established disease and increase the risk of progression (9), it is important to understand the chronology of events so that individual lesions can be tackled early and progression to more advanced stages can be avoided. Although hyaline articular cartilage loss is one of the structural disease hallmarks, the evidence that joint deterioration begins with cartilage pathology is sparse (1). Several authors have suggested that incidental meniscal pathology might be one of the main triggers of disease onset (10); however, the role of the meniscus in disease onset is under debate (11,12). Synovial activation, which is reflected on MRI as joint effusion and synovial thickening, appears to increase the risk of cartilage loss and might play a crucial yet not fully understood role in early disease (13–15). Furthermore, the subchondral bone seems to be an important driver of disease progression, and studies in animal models have suggested that bone marrow changes might be the earliest structural manifestation of disease onset (16). Finally, prevalent cartilage damage and focal defects markedly increase the risk of further progression; indeed, such lesions might still be one of the most important triggers of progression on a subregional level and later also at the joint level, leading to manifest radiographic OA (9,17). Eventually, a more or less concomitant appearance of these lesions may be possible (8).

The purpose of the present study was to test the hypotheses that 1) the presence of MRI-based measures of structural joint tissue damage, including cartilage, subchondral bone, menisci, and synovium, differ between knees that developed incident radiographic OA and matched control knees that did not develop radiographic OA during the 48 months prior to developing disease, 2) the incidence and fluctuation of abnormal structural features prior to developing disease differ between cases and controls, and, finally, 3) the cumulative presence of abnormal structural features increases the risk of incident radiographic OA.

PATIENTS AND METHODS

The Osteoarthritis Initiative. The OAI is an ongoing longitudinal cohort study designed to identify biomarkers of the onset and/or progression of knee OA. Both knees of 4,796 participants were studied using 3T MRI and fixed-flexion radiography at baseline and at 12, 24, 36, and 48 months (18). OAI participants were 45–79 years old at baseline and had symptomatic knee OA in at least 1 knee or were at increased risk of developing symptomatic knee OA with the presence of ≥2 of the following risk factors: being overweight, history of knee injury or surgery, family history of knee replacement, or Heberden's nodes. General exclusion criteria were presence of rheumatoid arthritis or other inflammatory arthritis, bilateral end-stage knee OA, inability to walk without aids, and MRI contraindications. Patients were recruited at 4 clinical sites in

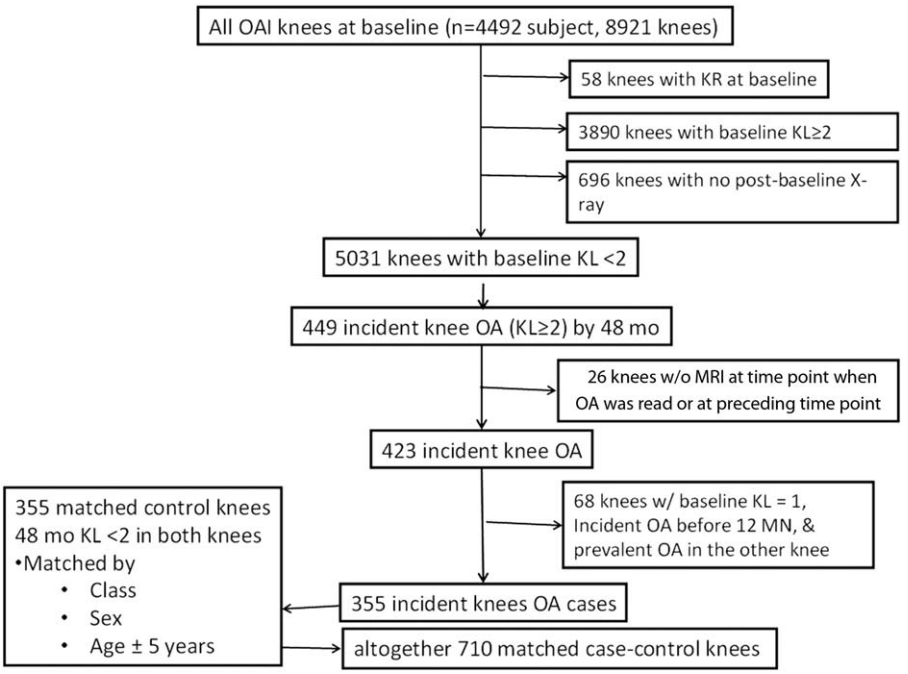

Figure 1. Flow chart showing inclusion of study subjectes/knees. Class refers to the Kellgren/Lawrence (K/L) score for radiographic osteoarthritis (OA). OAI = Osteoarthritis Initiative; KR = knee replacement; MRI = magnetic resonance imaging; MN = months.

the US. The institutional review board at each of the sites approved the study, and informed consent was obtained from all participants.

Radiography. OAI knee radiographs were acquired using a posteroanterior fixed-flexion weight-bearing protocol (19,20) and a Plexiglas positioning frame (SynaFlexer; Synarc) (21). The K/L grade was determined by central readings of baseline serial fixed-flexion knee radiographs (22). For each subject, all radiographs were read paired. The weighted kappa for inter-reader agreement was 0.79 for K/L grade. Prespecified discrepancies were adjudicated in a consensus session with a third reader (22).

Selection of case and control knees. Cases were defined as study participants who had at least 1 knee that developed incident radiographic OA during the 4 years of followup. Incident radiographic OA was defined as the first occurrence of radiographic findings compatible with OA (K/L grade of ≥2 on the posteroanterior view) during the course of the study. This time point was called P0, with P −1 being defined as the time point 1 year prior to the detection of radiographic OA, P −2 defined as 2 years prior to the detection of radiographic OA, P −3 defined as 3 years prior to the detection of radiographic OA, and P −4 defined as 4 years prior to the detection of radiographic OA. All participants with available images at the time point when incidence was read or the time point prior to fulfilling the case definition were included. An identical number of control knees were selected from knees that did not develop incident radiographic OA during the study period. The control knees were matched to case knees according to sex, age (within 5 years), and contralateral knee OA status (i.e., K/L grade 0, 1, or 2+ in the other knee). Each case was matched to a control knee from a subject who was at risk at the time of case occurrence and had available images at the relevant time points, whether this was at 12, 24, 36, or 48 months of followup. Both case and control knees had K/L scores of 0 or 1 at baseline. A detailed overview of subject inclusion is presented as a flow chart in Figure 1.

MRI acquisition. MRI of both knees was performed on 3T systems (Siemens Trio) at the 4 OAI clinical sites. MRIs were acquired with a dedicated quadrature transmit/receive knee coil using a coronal intermediate-weighted 2-dimensional turbo spin-echo sequence, a sagittal 3-dimensional dual-echo steady-state sequence, and a sagittal intermediate-weighted fat-suppressed turbo spin-echo sequence. Additional parameters of the full OAI pulse sequence protocol and the sequence parameters have been published in detail previously (18).

MRI assessment. Two musculoskeletal radiologists, one with 11 years of experience (FWR) and the other with 14 years of experience (AG) in semiquantitative assessment of knee OA, who were blinded with regard to clinical data and case–control status, read the MRIs according to a validated scoring system (23). Baseline and followup MRIs were read with the chronological order known to the readers. Each reader scored half of the MRIs, including both cases and controls, and readers were blinded with regard to case or control status. The following joint features were assessed: cartilage morphology, subchondral bone marrow lesions (BMLs), meniscal status, meniscal extrusion, Hoffa synovitis, and effusion synovitis (Figure 2).

Cartilage was scored in 14 articular subregions (5 subregions in the medial and lateral tibiofemoral compartments and 4 subregions in the patellofemoral compartment), incorporating area size per subregion (from 0 to 3) and percentage of subregion that was affected by full-thickness cartilage loss (from 0 to 3).

BMLs were assessed on a scale of 0–3 in the same 14 subregions, taking into account the percentage of a subregion that was affected by BML (i.e., lesion size). Since the scoring

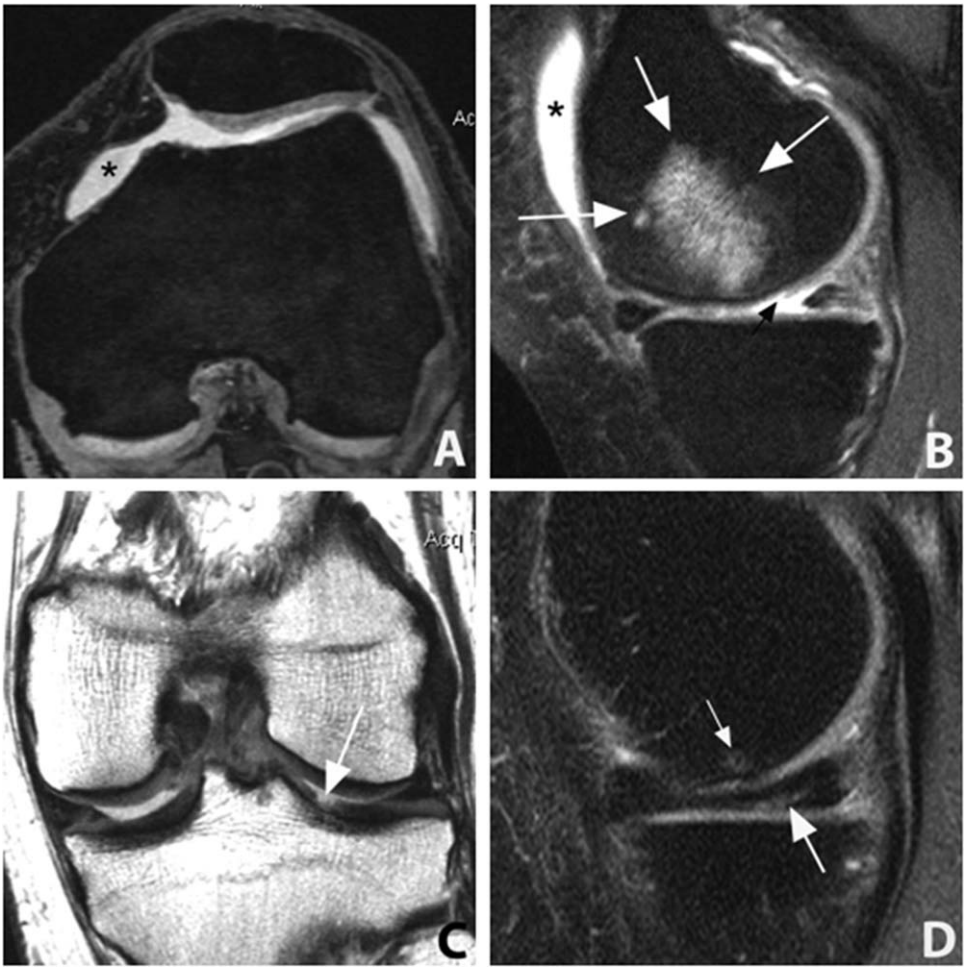

Figure 2. Examples of the different magnetic resonance imaging (MRI)–detected risk factors in knees without radiographic osteoarthritis. **A,** Effusion synovitis. Axial double-echo steady-state image shows intraarticular hyperintensity (**asterisk**) and slight distension of the joint capsule, reflecting effusion synovitis. **B,** Bone marrow lesion (BML). Sagittal intermediate-weighted fat-suppressed image shows a large BML in the central subregion of the medial femur (**white arrows**). Note additional concomitant MRI features including effusion synovitis (**asterisk**) and superficial focal cartilage damage (**black arrow**). **C,** Cartilage damage. Coronal intermediate-weighted image shows a focal full-thickness cartilage defect in the lateral tibial plateau (**arrow**). **D,** Meniscal damage. Sagittal intermediate-weighted fat-suppressed image depicts a degenerative horizontal-oblique meniscal tear of the posterior horn of the medial meniscus (**large arrow**). Note that in addition, there is a small subchondral BML in the central medial femur (**small arrow**), but no adjacent cartilage damage.

system used only uses one parameter of lesion size, which incorporates both cystic and ill-defined parts of BMLs in a given subregion, analysis of subchondral cysts was included in the definition of BMLs. Meniscal status was scored in the anterior horn, body segment, and posterior horn of the medial and lateral menisci on a scale of 0–8, taking into account intrameniscal signal changes, different types of meniscal tears, and meniscal maceration, i.e., substance loss. Meniscal extrusion was scored in the coronal planes on a scale of 0–3, where 2 = an extrusion $\geq$3 mm. Signal alterations in the intercondylar region of Hoffa's fat pad were scored on a scale of 0–3 as a surrogate for synovial thickening termed Hoffa synovitis. Joint effusion (also called effusion synovitis since it is not possible to discern joint fluid from synovial thickening on MRI) was graded on a scale of 0–3 in terms of the estimated maximal distention of the synovial cavity.

One radiologist (FWR) rescored 20 randomly chosen MRIs in random order for the same features after a 4-week interval to determine intrareader reliability. Interobserver reliability between the 2 readers was assessed using the same 20 cases. Summarizing the intra- and interobserver reliability results, all of the measures showed substantial (0.61–0.8) or almost perfect (0.81–1.0) agreement (24). A detailed overview of the reliability results is available from the author upon request.

Statistical analysis. Analyses were performed at the compartmental and knee level using several analytic approaches. Conditional logistic regression was used to assess the risk of incident radiographic OA related to the presence of structural parameters at each individual time point for a maximum of 4 time points (i.e., 4 years) prior to the case-defining visit when incident radiographic OA was established. Based on the available literature on the relevance of each feature for potential structural progression

Table 1. Risk of incident radiographic OA in relation to the presence of MRI structural features over 4 years prior to the diagnosis of radiographic OA*

	P −4			P −3			P −2			P −1		
MRI biomarker	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA
Any Hoffa synovitis	26 (52.0)	16 (32.0)	1.91 (0.91–4.00)	75 (51.4)	70 (48.0)	1.16 (0.71–1.90)	122 (56.0)	93 (42.7)	1.76 (1.18–2.64)†	195 (59.3)	127 (38.5)	2.42 (1.71–3.42)†
Any effusion synovitis	26 (52.0)	21 (42.0)	1.71 (0.68–4.35)	68 (46.6)	62 (42.5)	1.21 (0.73–2.02)	114 (52.3)	88 (40.4)	1.81 (1.18–2.78)†	194 (58.8)	128 (38.8)	2.50 (1.76–3.54)†
BML score ≥2												
Medial	3 (6.0)	1 (2.0)	3.00 (0.31–28.8)	5 (3.4)	1 (0.7)	5.00 (0.58–42.8)	13 (6.0)	4 (1.8)	3.25 (1.06–9.97)	26 (7.9)	4 (1.2)	6.50 (2.27–18.62)†
Lateral	1 (2.0)	0 (0.0)	NA	5 (3.4)	3 (2.1)	1.67 (0.40–6.97)	8 (3.7)	5 (2.3)	1.60 (0.52–4.89)	16 (4.9)	7 (2.1)	2.29 (0.94–5.56)
PFJ	18 (36.0)	12 (24.0)	1.67 (0.73–3.81)	45 (30.8)	40 (27.4)	1.19 (0.70–2.01)	70 (32.1)	60 (27.5)	1.24 (0.82–1.90)	104 (31.5)	83 (25.2)	1.36 (0.96–1.94)
Whole knee (excluding PFJ)	3 (6.0)	1 (2.0)	3.00 (0.31–28.8)	9 (6.2)	4 (2.7)	2.25 (0.69–7.31)	19 (8.7)	9 (4.1)	2.25 (0.98–5.18)	38 (11.5)	11 (3.3)	3.70 (1.84–7.44)†
Whole knee	20 (40.0)	13 (26.0)	1.88 (0.80–4.42)	50 (34.3)	43 (29.5)	1.26 (0.75–2.11)	84 (38.5)	66 (30.3)	1.46 (0.96–2.22)	130 (39.4)	91 (27.6)	1.66 (1.19–2.33)†
Cartilage damage score ≥1.1												
Medial	10 (20.0)	21 (42.0)	0.31 (0.11–0.85)	33 (22.6)	37 (25.3)	0.85 (0.50–1.46)	65 (29.8)	62 (28.4)	1.08 (0.69–1.68)	129 (39.1)	94 (28.5)	1.71 (1.20–2.46)†
Lateral	11 (22.0)	10 (20.0)	1.13 (0.43–2.92)	37 (25.3)	38 (26.0)	0.96 (0.55–1.68)	56 (25.7)	55 (25.2)	1.03 (0.64–1.64)	107 (32.4)	93 (28.2)	1.24 (0.86–1.77)
PFJ	33 (66.0)	33 (66.0)	1.00 (0.40–2.51)	96 (65.8)	98 (67.1)	0.94 (0.57–1.54)	154 (70.6)	139 (63.8)	1.40 (0.91–2.13)	245 (74.2)	222 (67.3)	1.44 (1.01–2.06)
Whole knee (excluding PFJ)	18 (36.0)	29 (58.0)	0.27 (0.09–0.80)	56 (38.4)	67 (45.9)	0.69 (0.42–1.14)	99 (45.4)	101 (46.3)	0.96 (0.62–1.49)	188 (57.0)	160 (48.5)	1.49 (1.05–2.12)
Whole knee	39 (78.0)	42 (84.0)	0.57 (0.16–2.08)	117 (80.1)	120 (82.2)	0.84 (0.43–1.64)	182 (83.5)	175 (80.3)	1.27 (0.73–2.20)	291 (88.2)	267 (80.9)	1.86 (1.16–2.99)
Meniscus damage score ≥2												
Medial, any tear or maceration	14 (28.0)	16 (32.0)	0.80 (0.32–2.03)	40 (27.4)	36 (24.7)	1.17 (0.67–2.03)	76 (34.9)	51 (23.4)	1.83 (1.17–2.89)†	132 (40.0)	81 (24.6)	2.19 (1.50–3.18)†
Lateral, any tear or maceration	11 (22.0)	6 (12.0)	2.00 (0.66–6.06)	21 (14.4)	14 (9.6)	1.64 (0.76–3.52)	34 (15.6)	24 (11.0)	1.56 (0.85–2.84)	53 (16.1)	40 (12.1)	1.50 (0.91–2.46)
Medial extrusion	2 (4.0)	4 (8.0)	0.33 (0.04–3.21)	5 (3.4)	8 (5.5)	0.57 (0.17–1.95)	15 (6.9)	11 (5.1)	1.40 (0.62–3.15)	31 (9.4)	22 (6.7)	1.47 (0.82–2.64)
Lateral extrusion	1 (2.0)	0 (0.0)	NA	1 (0.68)	1(0.68)	1.00 (0.06–15.99)	3 (1.38)	1 (0.5)	3.00 (0.31–28.84)	3 (0.9)	2 (0.6)	1.50 (0.25–8.98)

* Except where indicated otherwise, values are the hazard ratio (95% confidence interval). MRI = magnetic resonance imaging; P −4 = 4 years prior to the detection of radiographic osteoarthritis (OA); BML = bone marrow lesion; NA = not applicable; PFJ = patellofemoral joint.
† $P < 0.01$.

and on the personal experience of the authors, the presence of structural features was defined as any effusion or Hoffa synovitis (score of ≥1), moderate and large BMLs (score of ≥2), moderate and severe cartilage damage (score of ≥1.1), meniscal tear or maceration (score of ≥2), and presence of medial and lateral meniscal extrusion in the coronal plane (score of ≥2) (8,13, 25–31). In addition, the risk of incident radiographic OA was assessed for the presence of these same features at the baseline visit, at the case-defining visit (P0), and at any of the time points assessed from P −4 to P0 and from P −4 to P −1, the visit before the case-defining visit.

Further, we stratified knees into those that did not exhibit a given feature at any of the time points (i.e., absent), those in which the feature was incident (i.e., was not present at baseline but was present at least at 1 of the followup time points and all subsequent relevant time points with available images until P0), those in which the feature was variable (i.e., was present at least at 1 of the time points but not all of them), and those in which the feature was prevalent (i.e., exhibited a feature at all time points). We assessed risk of incident radiographic OA for each of these subgroups, using the group that did not exhibit a feature at any of the time points as the reference. Finally, the risk of incident radiographic OA was determined, including the number of features present at a given time point, differentiating 6 structural features (Hoffa synovitis, effusion synovitis, BMLs, cartilage damage, meniscal damage, and meniscal extrusion), with the same cutoffs as described above and using the presence of no feature or only 1 feature as the reference.

Because we tested up to 5 different codings for each feature, we used a Bonferroni adjustment of 5 to the 2-tailed significance level of 0.05. Weighted kappa statistics were applied to determine inter- and intraobserver reliability. All statistical calculations were performed using Stata/IC 11.2 for Windows (StataCorp) and SAS 9.3.

RESULTS

A total of 355 case knees and 355 matched control knees were included. Participants had a mean ± SD age of 60.2 ± 8.6 years, were predominantly female (66.5%), and were overweight (mean ± SD body mass index [BMI] 28.3 ± 4.4 kg/m^2). No differences were observed for age and sex, but cases had a slightly higher BMI compared to controls (28.9 kg/m^2 versus 27.7 kg/m^2; $P = 0.001$). Eighty-four percent of the subjects were white, and there were no significant differences with regard to ethnicity between the case and control groups. Of the matched pairs, 63 (17.8%) had a baseline K/L grade of 0 in both knees, 76 (21.4%) had a baseline K/L grade of 0 in one knee and 1 in the contralateral knee, 83 (23.4%) had a baseline K/L grade of 1 in both knees, 59 (16.6%) had a baseline K/L grade of 0 in one knee and ≥2 in the contralateral knee, and 74 (20.9%) had a baseline K/L grade of 1 in one knee and ≥2 in the contralateral knee. The case-defining visit of radiographic OA incidence was 12 months for 119 knees (33.5%), 24 months for 83 knees (23.4%), 36 months for 103 knees (29.0%), and 48 months for 50 knees (14.1%).

The trajectory of the presence of structural damage at specific time points from 1 to 4 years prior to incident radiographic OA showed that at 2 years prior to the case-defining visit (P −2), the presence of Hoffa synovitis (hazard ratio [HR] 1.76 [95% confidence interval (95% CI) 1.18–2.64]), effusion synovitis (HR 1.81 [95% CI 1.18–2.78]), and medial meniscal damage (HR 1.83 [95% CI 1.17–2.89]) increased the risk of incident radiographic OA. One year prior to the case-defining visit, multiple structural features predicted incident radiographic OA 1 year later, with the strongest risk factors being medial BMLs (HR 6.50 [95% CI 2.27–18.62]) and any tibiofemoral BMLs (HR 3.70 [95% CI 1.84–7.44]) and effusion synovitis (HR 2.50 [95% CI 1.76–3.54]). With regard to earlier time points, there was a trend toward the presence of Hoffa synovitis at P −4 increasing the risk of incident radiographic OA, but this finding did not reach statistical significance. The detailed results of the trajectory over time are presented in Table 1.

We also examined the impact of the presence of structural damage across multiple time points. Focusing on the baseline visit, medial and whole knee BMLs and Hoffa and effusion synovitis increased the risk of OA, while at the time point of incident radiographic OA (P0) all structural features were significant except for patellofemoral BMLs (HR 1.41 [95% CI 0.98–2.03]) and lateral meniscal extrusion (HR 5.50 [95% CI 1.22–24.81]). When all time points were combined (a feature being positive at any of the analyzed time points from P −4 to P0), the presence of any of the features, except for patellofemoral BMLs and lateral extrusion, increased the risk of incident radiographic OA. Incorporating only the time points from P −4 to P −1, many features remained significant, except for lateral and patellofemoral BMLs and cartilage damage, lateral meniscal damage, and any meniscal extrusion. Table 2 presents these results in detail.

The relevance of the fluctuation and incidence of features over time for the development of incident radiographic OA was investigated by examining the time points at which a feature was never present (i.e., absent, as the referent group), variably present (i.e., fluctuating), incident, or always present (i.e., prevalent). Knees in which the presence of the feature was incident (e.g., not found at baseline but present for at least 1 subsequent time point and all subsequent time points from P −4 to P0) showed the most highly increased risk (e.g., odds ratio [OR] 12.09 [95% CI 4.33–33.77] for cartilage damage and OR 9.52 [95% CI 3.94–22.99] for Hoffa synovitis), and the group with all time points positive showed a lesser risk (e.g., OR 3.53 [95% CI 1.92–6.49] for cartilage damage and OR 2.50 [95% CI 1.73–3.60] for Hoffa synovitis). The details of this analysis are presented in Table 3.

We examined the impact of the concomitant presence of multiple structural features of joint

Table 2. Risk of incident radiographic OA in relation to the presence of MRI-detected joint damage at baseline, at diagnosis, and for all time points combined*

	Baseline (n = 710 knees)			P0 (n = 670 knees)			Ever (P −4 to P0) (n = 710 knees)			Ever (P −4 to P −1) (n = 710 knees)		
MRI biomarker	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA	Cases, no. (%)	Controls, no. (%)	Risk of incident radiographic OA
Any Hoffa synovitis	191 (54.0)	137 (38.6)	1.90 (1.37–2.63)†	208 (62.3)	131 (39.2)	2.71 (1.90–3.87)†	230 (64.8)	147 (41.4)	2.77 (1.95–3.92)†	212 (59.7)	143 (40.3)	2.26 (1.63–3.12)†
Any effusion synovitis	174 (49.0)	138 (38.9)	1.62 (1.18–2.23)†	216 (64.5)	137 (40.9)	2.98 (2.08–4.26)†	268 (75.5)	189 (53.2)	3.39 (2.29–5.02)†	222 (62.5)	163 (45.9)	2.23 (1.58–3.15)†
BML score ≥2												
Medial	21 (5.9)	5 (1.4)	4.20 (1.58–11.14)†	58 (17.3)	11 (3.3)	6.22 (3.10–12.51)†	74 (20.9)	15 (4.2)	5.92 (3.24–10.81)†	32 (9.0)	9 (2.5)	3.88 (1.78–8.43)†
Lateral	11 (3.1)	7 (2.0)	1.57 (0.61–4.05)	28 (8.4)	7 (2.1)	4.00 (1.73–9.27)†	38 (10.70)	12 (3.4)	3.17 (1.64–6.11)†	22 (6.2)	10 (2.8)	2.20 (1.04–4.65)
PFJ	112 (31.6)	86 (24.2)	1.44 (1.02–2.03)	105 (31.4)	84 (25.2)	1.41 (0.98–2.03)	148 (41.7)	117 (33.0)	1.49 (1.07–2.08)	135 (38.0)	110 (31.0)	1.40 (1.00–1.95)
Whole knee (excluding PFJ)	28 (7.9)	12 (3.3)	2.46 (1.22–4.95)	80 (23.9)	18 (5.4)	5.13 (2.96–8.91)†	101 (28.5)	27 (7.6)	4.36 (2.76–6.91)†	48 (13.5)	19 (5.4)	2.71 (1.55–4.72)†
Whole knee	130 (36.6)	95 (26.8)	1.60 (1.14–2.26)†	155 (46.3)	94 (28.1)	2.36 (1.63–3.41)†	208 (58.6)	133 (37.5)	2.50 (1.77–3.53)†	166 (46.8)	121 (34.1)	1.74 (1.25–2.41)†
Cartilage damage score ≥1.1												
Medial	114 (32.1)	97 (27.32)	1.28 (0.91–1.81)	184 (54.9)	112 (33.4)	2.53 (1.80–3.57)†	194 (54.7)	114 (32.1)	2.70 (1.93–3.79)†	137 (38.6)	105 (29.6)	1.56 (1.11–2.19)†
Lateral	110 (31.0)	95 (26.8)	1.25 (0.88–1.77)	138 (41.2)	92 (27.5)	1.96 (1.36–2.82)†	146 (41.1)	100 (28.2)	1.84 (1.30–2.59)†	119 (33.5)	98 (27.6)	1.34 (0.95–1.91)
PFJ	251 (70.7)	233 (65.6)	1.29 (0.92–1.81)	264 (78.8)	226 (67.5)	1.86 (1.29–2.69)†	278 (78.3)	244 (68.7)	1.71 (1.20–2.44)†	263 (74.1)	240 (67.6)	1.40 (1.00–1.97)
Whole knee (excluding PFJ)	181 (51.0)	164 (46.2)	1.24 (0.90–1.72)	256 (76.4)	170 (50.8)	3.61 (2.42–5.38)†	270 (76.1)	179 (50.4)	3.53 (2.41–5.18)†	204 (57.5)	173 (48.7)	1.51 (1.08–2.11)
Whole knee	299 (84.2)	283 (79.7)	1.42 (0.92–2.19)	316 (94.3)	275 (82.1)	4.15 (2.24–7.71)†	335 (94.4)	293 (82.5)	4.00 (2.20– 7.29)†	315 (88.7)	288 (81.1)	1.93 (1.21–3.07)†
Meniscus damage score ≥2												
Medial, any tear or maceration	115 (32.4)	85 (23.9)	1.60 (1.11–2.31)	170 (50.8)	85 (25.4)	3.07 (2.13–4.43)†	178 (50.1)	91 (25.6)	2.93 (2.07–4.16)†	139 (39.2)	89 (25.1)	2.02 (1.42–2.88)†
Lateral, any tear or maceration	49 (13.8)	41 (11.6)	1.26 (0.78–2.03)	71 (21.2)	40 (11.9)	2.29 (1.41–3.72)†	72 (20.3)	43 (12.1)	2.12 (1.32–3.39)†	59 (16.6)	42 (11.8)	1.61 (1.00–2.59)
Medial extrusion	18 (5.1)	23 (6.5)	0.76 (0.40–1.46)	90 (26.9)	27 (8.1)	4.32 (2.62–7.12)†	94 (26.5)	28 (7.9)	4.30 (2.64–7.01)†	32 (9.0)	26 (7.3)	1.26 (0.73–2.18)
Lateral extrusion	4 (1.1)	2 (0.6)	2.00 (0.37–10.92)	11 (3.9)	2 (0.6)	5.50 (1.22–24.81)	11 (3.1)	2 (0.6)	5.50 (1.22–24.81)	5 (1.4)	2 (0.6)	2.50 (0.49–12.89)

* Except where indicated otherwise, values are the hazard ratio (95% confidence interval). MRI = magnetic resonance imaging; P0 = first occurrence of radiographic findings compatible with osteoarthritis (OA); P −4 =4 years prior to the detection of radiographic osteoarthritis; BML = bone marrow lesions; PFJ = patellofemoral joint.
† $P < 0.01$.

Table 3. Time points at which knees exhibited the features of interest*

MRI biomarker	Cases, no. (%)	Controls, no. (%)	OR (95% CI)
Hoffa synovitis			
Absent	125 (35.2)	208 (58.6)	Reference
Fluctuating	8 (2.3)	6 (1.7)	1.89 (0.56–6.41)
Incident	39 (11.0)	10 (2.8)	9.52 (3.94–22.99)†
Prevalent	183 (51.6)	131 (36.9)	2.50 (1.73–3.60)†
Effusion synovitis			
Absent	87 (24.5)	166 (46.8)	Reference
Fluctuating	37 (10.4)	43 (12.1)	2.02 (1.15–3.55)
Incident	94 (26.5)	51 (14.4)	4.54 (2.71–7.60)†
Prevalent	137 (38.6)	95 (26.8)	3.47 (2.23–5.41)†
Bone marrow lesion			
Absent	147 (41.4)	222 (62.5)	Reference
Fluctuating	34 (9.6)	28 (7.9)	1.96 (1.11–3.45)
Incident	78 (22.0)	38 (10.7)	3.18 (1.95–5.17)†
Prevalent	96 (27.0)	67 (18.9)	2.32 (1.53–3.52)†
Cartilage damage			
Absent	20 (5.6)	62 (17.5)	Reference
Fluctuating	1 (0.3)	2 (0.6)	1.77 (0.15–21.01)
Incident	36 (10.1)	10 (2.8)	12.09 (4.33–33.77)†
Prevalent	298 (83.9)	281 (79.2)	3.53 (1.92–6.49)†
Medial meniscus damage			
Absent	177 (49.9)	264 (74.4)	Reference
Fluctuating	0 (0.0)	1 (0.3)	NA
Incident	63 (17.8)	6 (1.7)	14.01 (5.47–35.87)†
Prevalent	115 (32.4)	84 (23.7)	1.91 (1.31–2.79)†
Lateral meniscus damage			
Absent	283 (79.7)	312 (87.9)	Reference
Fluctuating	0 (0.0)	2 (0.6)	NA
Incident	23 (6.5)	2 (0.6)	12.64 (2.81–56.81)†
Prevalent	49 (13.8)	39 (11.0)	1.62 (0.98–2.68)
Medial meniscus extrusion			
Absent	261 (73.5)	327 (92.1)	Reference
Fluctuating	0 (0.0)	0 (0.0)	NA
Incident	76 (21.4)	5 (1.4)	36.33 (8.89–148.47)†
Prevalent	18 (5.1)	23 (6.5)	0.881 (0.45–1.72)
Lateral meniscus extrusion			
Absent	344 (96.9)	353 (99.4)	Reference
Fluctuating	0 (0.0)	0 (0.0)	NA
Incident	7 (2.0)	0 (0.0)	NA
Prevalent	4 (1.1)	2 (0.6)	2.00 (0.37–10.92)

* A feature was considered absent if the knee did not exhibit that feature at any time point, fluctuating if the knee exhibited that feature at at least 1 of the time points including baseline but not all time points, incident if the knee did not exhibit the feature at baseline but exhibited it at at least 1 of the followup time points and at all subsequent time points, and prevalent if the knee exhibited the feature at all time points. MRI = magnetic resonance imaging; OR = odds ratio; 95% CI = 95% confidence interval; NA = not applicable.
† $P < 0.01$.

damage. An increasing number of positive features markedly increased the risk of radiographic OA, particularly for the baseline visits, the visits 2 years and 1 year prior to the case-defining visit, and the case-defining visit itself. Thus, the presence of 5 or 6 concomitant features 2 years prior to the diagnosis increased risk almost 6-fold, and the presence of 5 or 6 concomitant features 1 year prior to the diagnosis increased risk almost 12-fold compared to knees with only 1 feature or with no features present at the same time point. An increase in the number of concomitant features was highly associated with an increased risk of incident OA for the baseline, P −2, P −1, and P0 visits (P for trend <0.0001). The details of this analysis are presented in Table 4.

DISCUSSION

This is the first investigation to use a matched case–control design to examine structural predictors of incident radiographic OA over multiple time points from 1–4 years prior to incidence. Because the development

Table 4. Risk of incident radiographic osteoarthritis in relation to the number of MRI features present*

Assessment no. of features present per knee	Cases, no. (%)	Controls, no. (%)	OR (95% CI)
Baseline (n = 710)			
0 or 1	69 (19.4)	113 (31.8)	Reference
2	88 (24.8)	99 (27.9)	1.59 (1.01–2.51)
3	97 (27.3)	83 (23.4)	2.27 (1.41–3.65)†
4	68 (19.2)	47 (13.2)	2.79 (1.68–4.63)†
5 or 6	33 (9.3)	13 (3.7)	5.28 (2.35–11.86)†
P for trend			<0.0001
P −4 (n = 100)			
0 or 1	11 (22.0)	13 (26.0)	Reference
2	11 (22.0)	16 (32.0)	0.82 (0.26–2.54)
3	14 (28.0)	13 (26.0)	1.26 (0.40–3.98)
4	8 (16.0)	8 (16.0)	1.44 (0.38–5.43)
5 or 6	6 (12.0)	0 (0.0)	NA
P for trend			0.1042
P −3 (n = 292)			
0 or 1	30 (20.6)	38 (26.0)	Reference
2	43 (29.5)	43 (29.5)	1.39 (0.67–2.92)
3	38 (26.0)	34 (23.3)	1.57 (0.72–3.42)
4	26 (17.8)	22 (15.1)	1.59 (0.74–3.46)
5 or 6	9 (6.2)	9 (6.2)	1.40 (0.44–4.40)
P for trend			0.3105
P −2 (n = 436)			
0 or 1	40 (18.4)	68 (31.2)	Reference
2	48 (22.0)	54 (24.8)	1.70 (0.91–3.20)
3	56 (25.7)	52 (23.9)	2.23 (1.21–4.10)
4	49 (22.5)	34 (15.6)	2.75 (1.47–5.16)†
5 or 6	25 (11.5)	10 (4.6)	5.57 (2.13–14.57)†
P for trend			<0.0001
P −1 (n = 660)			
0 or 1	39 (11.8)	105 (31.8)	Reference
2	74 (22.4)	89 (27.0)	2.80 (1.60–4.91)†
3	89 (27.0)	77 (23.3)	4.57 (2.49–8.38)†
4	85 (25.8)	44 (13.3)	7.43 (4.06–13.6)†
5 or 6	43 (13.0)	15 (4.6)	11.93 (5.33–26.70)†
P for trend			<0.0001
P0 (n = 670)			
0 or 1	24 (7.2)	101 (30.2)	Reference
2	50 (14.9)	93 (27.8)	2.58 (1.35–4.94)†
3	81 (24.2)	75 (22.4)	7.57 (3.57–16.04)†
4	81 (24.2)	47 (14.0)	11.46 (5.70–3.03)†
5 or 6	99 (29.6)	19 (5.7)	38.48 (15.97–92.70)†
P for trend			<0.0001

* OR = odds ratio; 95% CI = 95% confidence interval; P −4 = 4 years prior to the detection of radiographic osteoarthritis; NA = not applicable; P0 = first occurrence of radiographic findings compatible with OA.
† $P < 0.01$.

of radiographic OA is a multifaceted process, we used several analytic approaches to assess the impact of the presence of MRI-detected features at different time points with regard to the risk of incident OA. Taking into account those different analyses, we found that knees exhibiting structural features in the 2 years prior to developing disease had an increased risk, with the number of features present increasing the risk further, i.e., lesion load seems potentially more relevant than the presence of any specific feature alone. With regard to the presence of features at baseline, it is noteworthy that the presence of BMLs, Hoffa synovitis, effusion synovitis, and prevalent medial meniscal damage increased the risk of OA while cartilage damage did not, although it was a common finding in both case and control knees at baseline. While our study design and the predefined annual followup visits within the OAI do not allow a definitive determination of the chronological order of the appearance of structural features, we showed that knees with new presence and persistence of a feature prior to the case-defining visit but not at baseline bear a higher risk than knees exhibiting that feature at every time point (prevalent findings),

suggesting that the incidence of new features over time might play a more important role than the presence of any given feature alone.

The latter finding in particular distinguishes our work from a recently published study also embedded within the OAI that looked specifically at the incidence of symptoms and cartilage loss over time as outcome parameters but only analyzed baseline predictors, with baseline being defined as the 12-month OAI visit (8). Our study is unique in that we looked at all available time points prior to the diagnosis of radiographic OA in a well-defined case–control design matched with regard to sex, age, and baseline radiographic disease status in both knees, which was paramount to ensure maximum comparability between cases and controls.

While the observed HRs are not easily compared due to relatively large and overlapping confidence intervals, nonetheless our trajectory analysis allows several important conclusions. We observed that the presence of MRI features seems to be particularly relevant closer to the diagnosis of radiographic OA, which underlines the relevance of fluctuation of these features, with some of the features that were observed long before the case-defining visit (i.e., 4 years or 3 years prior to the detection of radiographic OA) still potentially regressing and, thus, not contributing markedly to incident radiographic OA. An important finding was that at the visit 2 years prior to the case-defining visit (P −2), the presence of Hoffa and effusion synovitis, medial BMLs, and medial meniscal damage increased the risk of OA, but cartilage damage did not. This finding emphasizes the role of noncartilaginous features in early disease as well as disease progression, as has been suggested previously (9,13,32). The highest risk of any of the features at 1 year prior to the case-defining visit (P −1) was the presence of medial BMLs (more than 6-fold), suggesting that the presence of BMLs may be important later in the disease trajectory, when other features indicating structural damage are present.

At the time point of radiographic OA onset, knees that had developed radiographic OA were more likely to exhibit any of the MRI features except for patellofemoral BMLs, which was of borderline significance. This proves that OA is not a disease with a clearly defined onset, i.e., radiographic OA being the starting point, but rather a slowly developing process that seems to be well established by the time radiography is able to define it (i.e., K/L grade 2). In addition, lesion load plays an important role, with a higher risk of developing incident radiographic OA with the more features present, which again was true particularly for the 2 time points prior to the case-defining visit.

Our findings build on the existing literature and expand previous findings. Meniscal damage is a common finding in the elderly (11). Nonetheless, it has been reported that incidental meniscal damage is associated with a marked elevation in the subsequent risk of radiographic OA (10). Our findings support an important role of meniscal damage, including tears and any type of maceration, i.e., meniscal substance loss, in disease initiation. Meniscal extrusion has also been reported as a separate risk factor for disease progression (17,25), but our findings suggest that the role of extrusion does not seem to be as prominent in the onset of radiographic OA. We used a conservative cutoff of ≥3 mm for the definition of extrusion, which is consistent with the radiologic literature (26,27). A minor amount of extrusion might be within the physiologic range of normal, and thus not play a relevant role in disease onset.

Our work emphasizes the role of the subchondral bone in the disease course, as reflected by the highly increased risk in knees with medial BMLs. Again, we used a relatively conservative cutoff, with presence being defined as the presence of grade 2 or 3 lesions. BMLs are highly fluctuating, but most of the previous studies included smaller lesions in their analyses (33–35). The association of BMLs with pain has been particularly prominent for larger BMLs (35,36). Others reported that fluctuation of these lesions is highly associated with fluctuations in pain (37). We found that although fluctuating BMLs are associated with an increased risk of radiographic OA, persistent incident BMLs confer the greatest risk of radiographic OA. Microstructural changes within the subchondral bone alter the local biomechanics and load distribution, eventually leading to articular surface deformity, incident cartilage damage, and vice versa, emphasizing the close interrelationship within the osteochondral unit (33,38). The fact that cartilage damage played a lesser role in incident OA in our analyses supports the strategy of targeting the subchondral bone in early disease as an important treatment approach. We acknowledge as a shortcoming that subchondral sclerosis and thickening could not be assessed using the OAI MRI data set due to the lack of availability of a T1-weighted sequence. However, both features are manifestations of later disease stages, and it is unlikely that sclerosis is common in knees without radiographic OA, since sclerosis is one of the disease-defining features of the K/L scale.

OA is widely regarded as a biomechanically driven disease, with synovitis being a secondary phenomenon that further contributes to disease progression (39). We were not able to elucidate whether synovial activation is the very first manifestation of OA preceding other structural alterations, but we could confirm that inflammation

plays an important role in the later development of radiographic OA. The occurrence of incident Hoffa synovitis conferred very high odds (>9-fold) of incident radiographic OA. It has previously been shown that in knees without OA, the risk of cartilage loss was markedly increased whenever effusion and synovitis were present (13). A concomitant appearance of structural features in early disease has been suggested previously, with an increased risk of synovial activation in knees observed for knees with meniscal damage and no signs of OA at all (i.e., knees with a K/L grade of 0) (40).

Limitations of our study include the absence of information on symptomatic OA. We do not know if subjects who developed radiographic OA also developed symptoms and if subjects developed symptoms prior to the diagnosis of OA. Inclusion of these clinical parameters would have gone beyond the scope of this study, but they are highly important and need to be explored further. Recent work by Sharma and colleagues suggests an important role of several structural disease features in the development of symptoms (8). In addition, we included knees with K/L grades of 0 or 1 at baseline in our analyses, and it is unknown whether the results would differ if only knees with K/L grades of 0 at baseline had been included. We used cut points for the different MRI features that were based on potential clinical relevance and tried to be conservative (i.e., defining mainly moderate and large lesions as "presence" of a given feature). Different cut points might yield somewhat different results, which we acknowledge as a limitation. Performing multiple additional analyses using several cut points would have gone beyond the focus of our study.

In addition, we acknowledge that we were not able to contrast the findings of the MRI readings with a reference standard such as arthroscopy or histology. However, arthroscopy is able to visualize only the articular surface and misses evaluation of other important tissues such as the subchondral bone, and it is not feasible to invasively assess knee joints in an observational study over several time points. We applied a validated scoring system that was developed based on longstanding experience with other semiquantitative scoring instruments to assess structural joint damage in OA (23,41,42). The readers were highly experienced in MRI assessment, and the reliability of the readings was excellent.

Knee OA is a major public health concern, with a recent report estimating the lifetime risk of primary total knee replacement as 7.0% for men and as 9.5% for women. Over half of the adults in the US diagnosed as having symptomatic knee OA will potentially undergo a total knee replacement during their lifetime (43). The ultimate goal in any interventional approach must be a reduction of these numbers in light of aging populations, and targeting early disease seems to be one of the most promising approaches. Prior to development and implementation of therapeutic strategies, the structural determinants of disease need to be fully understood in order to target the most relevant tissue in any individual being affected by the disease. We acknowledge that OA is a multifactorial process and that disease onset may be triggered by pathology in multiple tissues that may be present or appearing not only in chronological order, but also concomitantly.

In summary, we demonstrated that knees exhibiting specific structural features of joint damge on MRI, especially within the 2 years prior to disease onset, exhibiting several features concomitantly, and experiencing the new occurrence of these features at one or more time points have an increased risk of developing incident radiographic OA as compared to matched knees not exhibiting these features of structural damage.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Roemer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Roemer, Kwoh, Hannon, Hunter, Eckstein, Boudreau, Guermazi.

Acquisition of data. Roemer, Kwoh, Hannon, Hunter, Guermazi.

Analysis and interpretation of data. Roemer, Kwoh, Hannon, Hunter, Eckstein, Fujii, Boudreau, Guermazi.

ADDITIONAL DISCLOSURES

Dr. Eckstein is an employee of Chondrometrics GmbH.

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